NOVEL SYNTHESIS OF IRBESARTAN

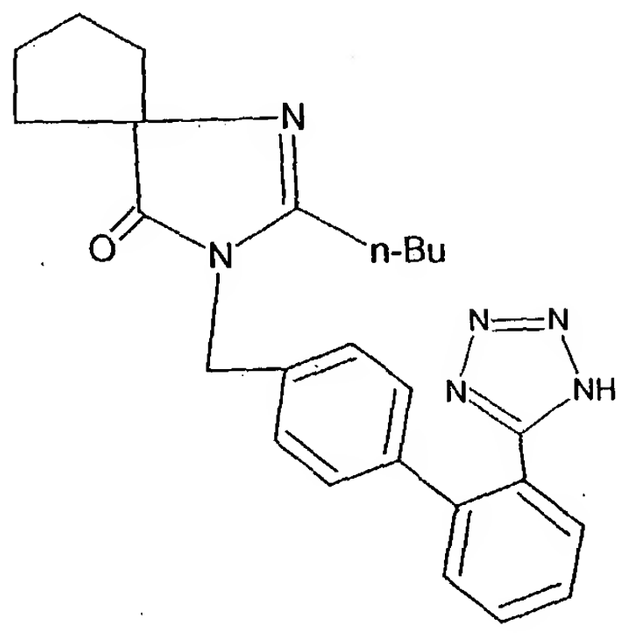
The present invention relates to a novel synthesis of irbesartan.

RELATED APPLICATIONS

The present Application claims the benefit of the filing date of United States Provisional Patent Applications 60/396,424, filed July 16, 2002, and 60/402,490, filed August 9, 2002.

BACKGROUND OF THE INVENTION

Irbesartan is a known angiotensin II receptor antagonist (blocker). Angiotensin is an important participant in the renin-angiotensin-aldosterone system (RAAS) and has a strong influence on blood pressure. The structure of irbesartan is shown below (I).



(I)

The synthesis of irbesartan is discussed, *inter alia*, in United States Patents 5,270,317 and 5,559,233; both of which are incorporated herein in their entirety by reference. In the synthesis therein disclosed, the prepenultimate reaction step (exclusive of work-up and purification) involves the reaction of a cyano group on the biphenyl ring with an azide, for example tributyltin azide. Reaction time as long as 210 hours can be required. *See,e.g.*, '317 patent.

United States Patent 5,629,331 also discloses a synthesis of irbesartan from a precursor 2-*n*-butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one with sodium azide using a dipolar aprotic solvent. As acknowledged in the '331 patent, there are safety risks involved in the use of azides (column 4, line 39). Also,

dipolar aprotic solvents (*e.g.* methyl pyrrolidone) are relatively high boiling and can be difficult to remove.

There is a need for an improved synthetic route to irbesartan.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a method of making irbesartan including the step of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system having first and second phases.

In another aspect, the present invention relates to a method of making irbesartan including the step of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system having first and second phases, wherein the first phase includes a first solvent that is an aromatic or aliphatic hydrocarbon and the second phase includes water and an inorganic base, for example KOH, NaOH, or LiOH, especially KOH.

In another aspect, the present invention relates to a method of making irbesartan including the step of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst that is a quaternary ammonium compound in a reaction system having first and second phases, wherein the first phase includes a first solvent that is an aromatic or aliphatic hydrocarbon and the second phase includes water and an inorganic base, for example KOH, NaOH, or LiOH, especially KOH.

In yet another aspect, the present invention relates to a method of making irbesartan including the steps of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of tetrabutylammonium hydrogensuflate in a reaction system having first and second phases, wherein the first phase includes a first solvent that is toluene and the second phase includes water and an inorganic base, especially KOH.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is schematic diagram of the process for making irbesartan of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel synthesis of irbesartan in a two-phase reaction system having first and second liquid phases. The reaction is carried out in the presence of a phase transfer catalyst.

The first and second phases include first and second solvents, respectively, which are substantially immiscible in each other so that, when combined in a reaction vessel, a two-phase system is formed. Solvents are substantially immiscible in each other when equal volumes of them are mixed together, a two-phase system is formed in which the volume of the two phases is essentially equal. Preferably, substantially immiscible solvents are soluble in each other to the extent of about 1% (weight basis) or less.

First solvents can be aromatic or aliphatic hydrocarbons. Preferred first solvents are aromatic hydrocarbons. Examples of preferred aromatic hydrocarbons include benzene, toluene, m-xylene, o-xylene, and the tetralins, to mention just a few. Other aromatic hydrocarbons useful in the practice of the present invention will be apparent to the skilled artisan. Toluene is a particularly preferred aromatic hydrocarbon for use as first solvent.

The second solvent includes water. Water can be used alone or, preferably, an inorganic base such as KOH, NaOH or LiOH, to mention just a few, is combined with the water. The preferred inorganic base is KOH. Preferably, the water of the second phase contains a molar amount of base that is about 7 to about 12 times the molar amount of the diazaspiro or biphenyl reactants discussed below.

Phase transfer catalysts are well known to one skilled in the art of organic synthesis. Phase transfer catalysts are of particular utility when at least first and second compounds to be reacted with each other have such different solubility characteristics that there is no practical common solvent for them and, accordingly, combining a solvent for one of them with a solvent for the other of them results in a two-phase system.

Typically, when such compounds are to be reacted, the first reactant is dissolved in a first solvent and the second reactant is dissolved in a second solvent. Because the solvent for the first reactant is essentially insoluble in the solvent for the second reactant, a two-phase system is formed and reaction occurs at the interface between the two phases. The rate of such an interfacial reaction can be greatly increased by use of a phase transfer catalyst (PTC).

Several classes of compounds are known to be capable of acting as phase transfer catalysts, for example quaternary ammonium compounds and phosphonium compounds, to mention just two. Tetrabutylammonium hydrogensulfate is a preferred PTC for use in the practice of present invention.

In a first step of the synthetic method of the present invention, 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one (IRB-03) is obtained. In this step, a first solution of 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole (IBR-02) in a first solvent is provided. IBR-02 is known in the art and is disclosed, for example, in United States Patent 5,128,355, the disclosure of which is incorporated herein in its entirety by reference.

Also to be provided is a second solution that includes 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one (IBR-01), water, PTC, and a base, preferably an inorganic base, most preferably, KOH. The base is present in an amount between about 7 and about 12 molar equivalents relative to the number of moles of IBR-01. 2-Butyl-1,3-diazaspiro[4.4]non-1-ene-4-one is known in the art and is disclosed, for example, in United States Patent 5,559,233, which has been incorporated herein by reference.

The first and second solutions, and their constituents, are combined in any order to form a two-phase reaction system that has first and second phases. The combining can be in any suitable vessel that is equipped with means for vigorous agitation of the reaction system to maximize the interfacial area between the two phases. The combining can be at any temperature from about 20° C to about 95° C, preferably at about 90°C. The reaction is allowed to proceed in the two phase system for a time that the skilled artisan will known to adjust according to the reaction temperature. When the reaction temperature is about 90° C, a reaction time between about 1 and about 2 hours is usually sufficient.

After the reaction time and to facilitate phase separation, the reaction system is allowed to cool, preferably to a temperature of about 15°C to about 30°C and the first (organic, aromatic hydrocarbon) and second (aqueous) phases are separated. If desired, the aqueous phase can be extracted one or more times with toluene and the extract(s) combined with the first (organic, aromatic hydrocarbon) phase. Solvent is removed from the separated first phase, preferably by evaporation, especially at reduced pressure, to afford a crude residue.

In a second step of the synthetic method of the present invention, the trityl group is cleaved from the tetrazole ring. Crude residue is dissolved in a suitable water-miscible solvent. A solvent is water miscible if it is miscible with water at least in any proportion from 80:20 to 20:80 (weight basis). Acetone is a preferred water-miscible solvent. The resulting solution is acidified, preferably with a mineral or sulfuric acid, and agitated at a temperature between about 15°C and about 30°C. The time of the cleavage reaction can be conveniently monitored using thin layer chromatography. The acid is neutralized (that is, the solution is basified) with a molar excess of base, preferably and inorganic base, most preferably aqueous KOH. The basification is to a pH of about 8 to about 12, preferably to a pH of about 9 to about 10.5. Water-miscible solvent is evaporated, preferably at reduced pressure, to concentrate the basified solution whereby a suspension id formed. The order of basification and evaporation is not important. That is, water-miscible solvent can be first evaporated, followed by basification of the concentrate.

The trityl alcohol formed is separated and the liquid phase is acidified (e.g. to a pH of about 2 to about 3.5), preferably with mineral acid, most preferably with HCl. The resulting suspension is cooled and the product recovered by, for example, filtration. If desired, the isolated product can be washed with an organic solvent, preferably a lower aliphatic alcohol, most preferably *iso*-propanol, and dried, preferably at reduced pressure.

In another embodiment, the present invention provides fine particle size or "micronized" irbesartan in

cluding a plurality of irbesartan particles wherein the mean particle size ($d_{.05}$) is about 2 μm to about 7 μm and 10 volume percent or less of the plurality of particles have a particle diameter equal to or greater than about 30 μm, preferably 20 μm.

Micronized irbesartan including a plurality of irbesartan particles can be obtained by comminution using a fluid energy mill, wherein the mean particle size ($d_{.05}$) produced is about 2 μm to about 7 μm and 10 volume percent or less of the plurality of particles have a particle diameter equal to or greater than about 10 μm..

A fluid energy mill, or "micronizer", is an especially preferred type of mill for its ability to produce particles of small size in a narrow size distribution, i.e., micronized material. As those skilled in the art are aware, micronizers use the kinetic energy of collision between particles suspended in a rapidly moving fluid (typically air) stream to cleave the particles. An air jet mill is a preferred fluid energy mill. The suspended particles are injected under pressure into a recirculating particle stream. Smaller particles are carried aloft inside the mill and swept into a vent connected to a particle size classifier such as a cyclone. The feedstock should first be milled to about 150 to 850 μm which may be done using a conventional ball, roller, or hammer mill.

The starting material may have an average particle size of about 20-100 microns.

The material is fed into the micronization system in a controlled feed rate by means of a screw feeder or a vibratory feeder. The air jet mill is operated with controlled air pressures. For the Microgrinding MC-500 KX, the feed rate is 40-80 kg/hr, the Feed air pressure is 6-8.5 bar and the grinding air is 3-6 bar.

Micronizationization can also be accomplished with a pin mill. The starting material may have an average particle size of about 20-100 microns. The material is fed into the mill system in a controlled feed rate by means of a screw feeder or a vibratory feeder. The mill is operated with controlled speed. For the Alpine UPZ 160, the feed rate is 60-75 kg/hr, the mill speed is 7,000-15,000 rpm.

Micronized irbesartan can be used to make pharmaceutical compositions that can be in the form of solid oral dosage forms, for example compressed tablets. Compressed tablets can be made by dry or wet granulation methods as is known in the art. In addition to the pharmaceutically active agent or drug, compressed tablets contain a number of pharmacologically inert ingredients, referred to as excipients. Some excipients allow or facilitate the processing of the drug into tablet dosage forms. Other excipients contribute to proper delivery of the drug by, for example, facilitating disintegration.

The present invention can be illustrated in one of its embodiments by the following non-limiting example.

Examples

Example 1:

A solution of KOH (10.4 g, 157.0 mmol), IRB-01 (12.0 g, 52.0 mmol) and Bu_4NHSO_4 (1.8g, 5.3 mmol) in water (40 mL) was added to a solution of IRB-02 (24.6 g, 44.1 mmol) in toluene (240 mL), and the resulting two-phase mixture was heated at 90°C with vigorous stirring for 1.5 hours. The mixture was cooled to room temperature, the phases were separated, and the aqueous phase was extracted with toluene (50mL). The combined organics were evaporated; the residue was dissolved in acetone (100 mL) and 3N HC1 (52 mL, 156 mmol, 3 eq) and stirred at room temperature (TLC monitoring). A solution of KOH (14.6 g, 260 mmol, 5 eq) in water (100 mL) was slowly added, and acetone was evaporated under reduced pressure. The precipitate formed (trityl alcohol) was filtered and washed with water (2 x 50 mL); the filtrate was washed with toluene and slowly acidified to pH 4 with 3N HCl. The resulting suspension was cooled to 0-4°C, stirred for additional 30 min and filtered. The cake was washed with cold *iso*-propanol (2 x 25 mL) and dried under reduced pressure at 50-60°C; affording crude IRB-00 (14.5g, 33.8 mmol). Yield 84.3%, purity 94% (by HPLC).

Example 2:

A solution of H_2SO_4 (98 %, 22.6 g, 12.3 mL, 0.225 mol, 1.5 eq) in water (160 mL) was added to a suspension of IRB-03 (100.6 g, 0.150 mol) in acetone (600 mL) at 35-40 °C and stirred for 7 h (suspension disappeared; TLC monitoring – Hexane / EtOAc = 1:1). Acetone was evaporated from the reaction mixture under reduced pressure at 30-40 °C.

Water (500 mL) was added to the resulting suspension. The resulting mixture was vigorously stirred and cooled to 0-5 °C. A solution of KOH (85 %, 39.6 g, 0.600 mol, 4 eq) in water (100 mL) was slowly added keeping the reaction temperature below 15 °C and the mixture was stirred for 30 min until a stable pH (9-10) was obtained. Then, a second portion of KOH (3.0 g, 50 mmol, 0.3 eq) in water (10 mL) was added and the reaction was stirred for additional 30 min at 5-10 °C (pH 10.5-11.5). The precipitate (triphenyl methanol) was filtered, washed with water (2 x 100 mL) and dried under reduced pressure (10 mmHg) at 50 °C to give 36.5 g (about 95 % yield) of triphenyl

methanol. The aqueous filtrate was extracted with ethyl acetate (300 mL), cooled to 10 °C and acidified to pH 2.0–3.5 with slow addition of 20 % aqueous H_2SO_4. The resulting suspension was stirred at 0-4 °C for an additional 30 min and filtered. The filter cake was washed twice with water (2 x 100 mL), then with EtOAc (100 mL) and dried under reduced pressure for 3 h at 50 °C afforded 60.0 g (93 % yield) of crude Irbesartan.

The crude product (60.0 g) was refluxed in 95 % aqueous ethanol (600 mL) for 1 h (clear solution was formed) and allowed to cool to room temperature with vigorous stirring. The mixture was stirred for an additional 2 h at 0-5 °C, filtered, and washed with cold 95 % aqueous ethanol (100 mL). The collected solid was dried under reduced pressure (3 h, 50 °C, 10 mmHg) afforded 56.0 g (93 % yield), of a white powder.